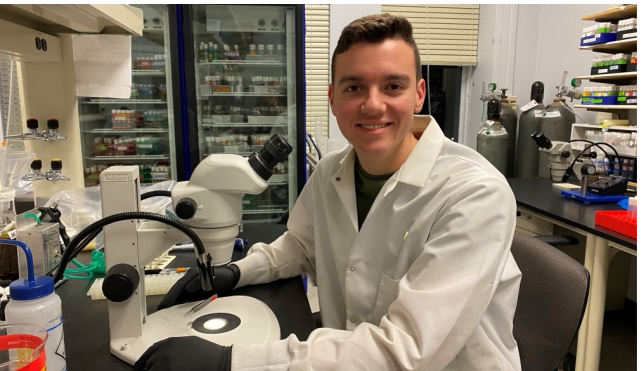
FORTITUDE™ Phase 1/2 Trial – Interim Results

Amy Halseth, PhD

Executive Director, Clinical Development

FSHD Connect Conference

June 15, 2024




Forward-Looking Statements

- "Forward-looking statements" are like educated guesses based on what we know now, but they're not sure things.
- This presentation includes predictions about future events or results, which are not guaranteed.
- These predictions are based on current expectations and could change due to many factors.
- We will not be providing an update on today’s presentation, even if new information becomes available later.
- The statements in this presentation are not promises, and what actually happens might be different, because lots of unexpected changes can come up.
- Even though we've made these statements thoughtfully, things may not go as planned, and our actual results could vary for reasons beyond our control.
- Our future performance is hard to predict and may not meet our or others' estimates.
- Don't rely too heavily on these statements; actual results could be different.

Avidity is Grateful for the Important Contributions that Paved the Way for the FORTITUDE™ Clinical Trial

We have leveraged the important progress made in developing a network of advocates, experts, knowledge, and tools including:

- FSHD Clinical Trial Research Network
- Natural History Studies including RESOLVE, MOVE, and MOVE+
- Patient Advocacy Organizations
- Community of Patients, Families, and Caregivers

AVIDITY® BIOSCIENCES

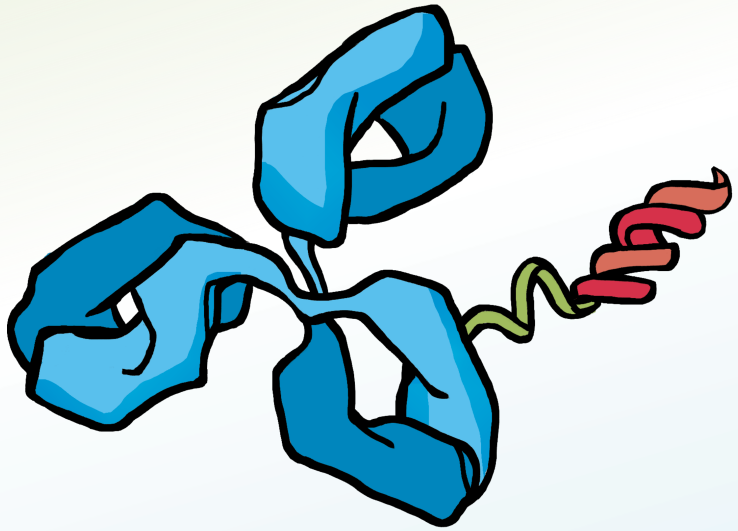
We want to thank each study participant, their families, the investigators, and their teams for their time, commitment, and continued contributions in the FORTITUDE™ study

AVIDITY® BIOSCIENCES

Amy
FSHD Advocate

We are committed to improving the lives of families impacted by rare diseases, including FSHD, through the development of new drugs.

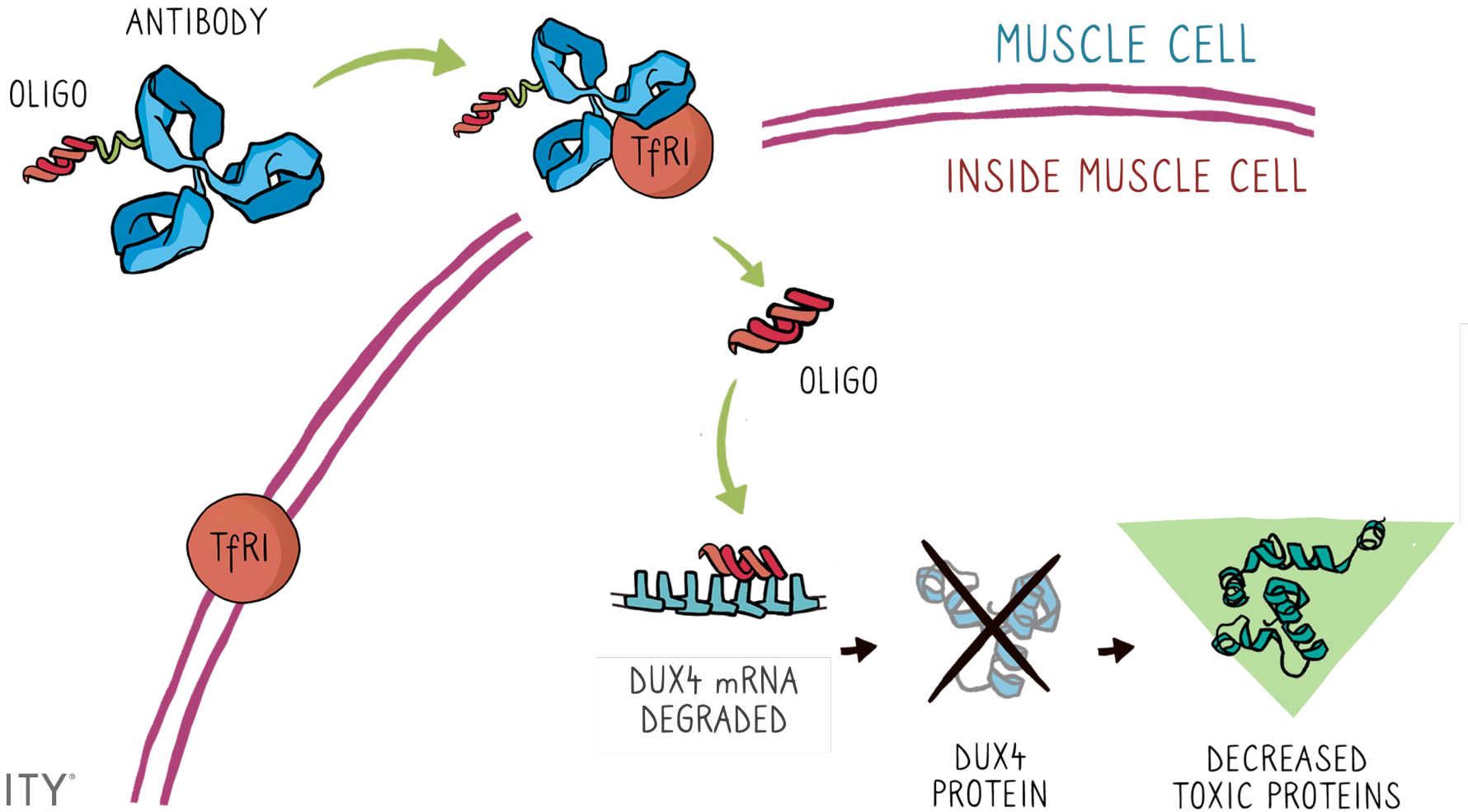
Announcing a New Name for Our Investigational Drug



- Former Name: **AOC 1020**
- Generic Name: ***delpacibart braxlosiran***
- Shortened Name: ***del-brax***

AVIDITY BIOSCIENCES

Del-brax is Designed to Target the Root Cause of FSHD



AVIDITY® BIOSCIENCES

FORTITUDE™

A Phase 1/2 Study of *del-brax* in Adults with FSHD

AVIDITY® BIOSCIENCES

FORTITUDE™ Phase 1/2 Study Overview & Goals

Designed in collaboration with patients, advocates, and expert physicians in the field

Study Overview

- FORTITUDE is a Phase 1/2 study of *del-brax*, a new investigational treatment for adults (ages 18-65) with FSHD
- Participants randomly assigned to receive multiple doses of either *del-brax* or placebo via IV infusion
  - Part A: 1 mg/kg, 2 mg/kg
  - Part B: 4 mg/kg
- Muscle biopsies and MRIs conducted during the study, and participants will be followed for up to 12 months
- Participants can roll over into an open label extension (OLE) study, where everyone will receive *del-brax*

Study Goals

- The primary goal of FORTITUDE is to evaluate the safety and tolerability of *del-brax*
- FORTITUDE also explores the effects of *del-brax* on DUX4-regulated gene expression, muscle strength, patient-reported outcomes, and quality of life measures

Baseline Demographics Generally Well Matched Between Groups

	Cohort A Placebo N=4 % or mean	*Del-brax* 2 mg/kg* N=8 % or mean
Sex, % Male	75	62.5
Age, years	53.5	51.6
Genetic Diagnosis, % FSHD 1	100	100
FSHD Clinical Score	9.3	9.3
D4Z4 Repeat Number	5.0	5.8
Age at First Symptom Onset (y)	25.3	28.6
Reachable Workspace RSA with weight (Q1+Q3) Reachable Workspace RSA without weight (Q1+Q3)**	0.118 0.156	0.088 0.138
Quantitative Muscle Testing - Percent Predicted Normal	33.97	30.14

*Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study
**Participants in FORTITUDE had >50% reduction in reachable workspace in Q1 & Q3 at baseline compared to normal controls (normal controls RWS (Q1+Q3) without weight: ~0.39, Han et al, 2015 Muscle Nerve)
Reachable Workspace (RWS) Relative Surface Area (RSA) (Q1+Q3) with or without weight was calculated using the average of both arms

AVIDITY BIOSCIENCES

FORTITUDE™

Del-brax: Favorable Safety and Tolerability

Subjects with ≥ 1 AE n (%)	Placebo N=13	2 mg/kg* N=8	4 mg/kg N=18
Any AE	11 (84.6%)	8 (100%)	17 (94.4%)
Related to study drug	3 (23.1%)	4 (50%)	9 (50%)
Severe AE	0	0	0
Serious AE (SAE)	0	0	0
AE leading to study discontinuation	0	0	0
AE leading to death	0	0	0

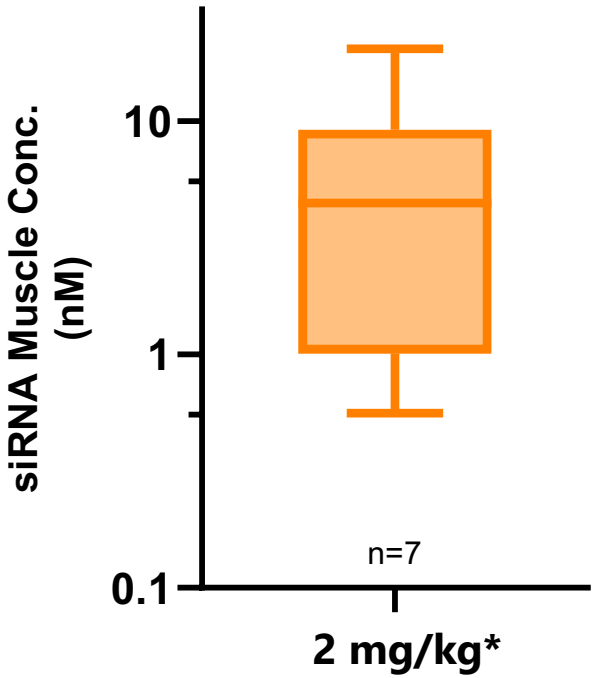
As of May 2024, data from FORTITUDE

All 39 patients enrolled remain in study

- No serious adverse events (AE), no severe AE
- No discontinuations
- All AE were mild or moderate
- Most common related AE occurring in 2 or more participants:
  - Fatigue
  - Rash
  - Hemoglobin decreased/anemia
  - Chills

*Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study

Del-brax: Consistent and Effective Delivery of siRNA to Muscle



Muscle biopsies were collected in leg muscles (vastus lateralis, vastus medialis, tibialis anterior, gastrocnemius medialis or gastrocnemius lateralis) with fat fraction 15-40%, 4 weeks after 3rd dose. *Doses were 1 mg/kg (D1), 2 mg/kg (D43 and D92). One participant in the del-brax treated group missed post-dose biopsy n=7

Evaluating Impact on DUX4 Levels using DUX4-Regulated Genes

- Inappropriate expression of the DUX4 gene is toxic to muscle cells resulting in FSHD symptoms
- It is challenging to measure DUX4, or a drug's impact on DUX4 directly
  - DUX4 is expressed at very low and sporadic levels in muscle cells
- Measuring DUX4-regulated gene expression makes it possible to evaluate a drug's effect on DUX4 levels
  - When DUX4 is turned on, it turns on other genes (DUX4-regulated genes)
  - DUX4-regulated genes have a prolonged signal

Avidity Gene Panel

LEUTX

TRIM43

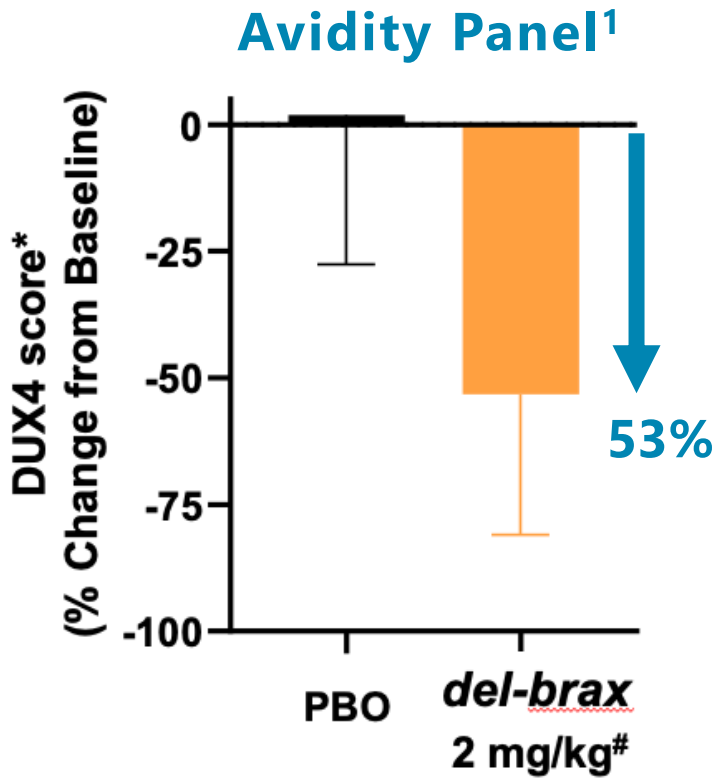
KHDC1L

MBD3L2

Reference genes: TBP, SPATA5

Del-brax Demonstrated Meaningful 53% Reduction in DUX4-regulated Genes

All *del-brax* treated participants showed reductions >20% in DUX4 regulated genes



1 Avidity 4-Gene panel (LEUTX, TRIM43, MBD3L2, KHDC1L, Reference genes: TBP, STATA5)

* DUX4 score in MRI informed muscle biopsy were determined utilizing qPCR (Avidity panel). DUX4 score calculated as cumulative expression of each gene and data presented as change at 4M treatment relative to cohort normalized baseline. Mean +/- SEM, N=7 del-brax, N=4 PBO. One participant in treated group did not receive post-treatment biopsy.

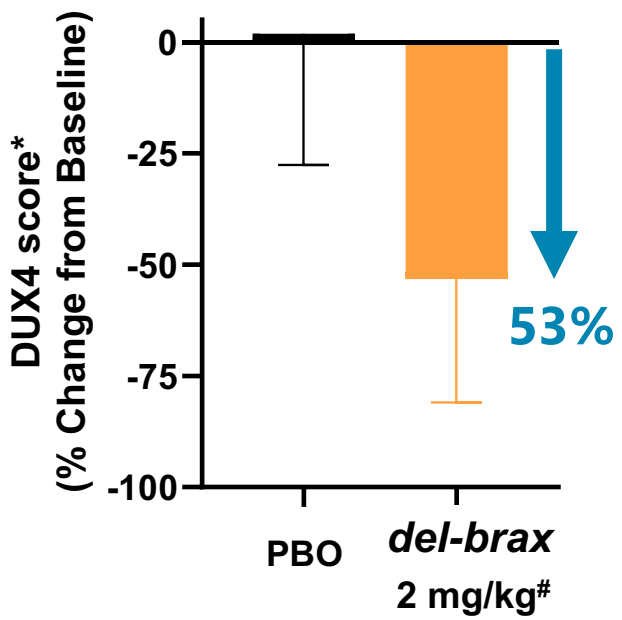
Doses were 1 mg/kg (D1), 2 mg/kg (D43 and D92) with biopsy 1 month after 3rd dose.

AVIDITY® BIOSCIENCES

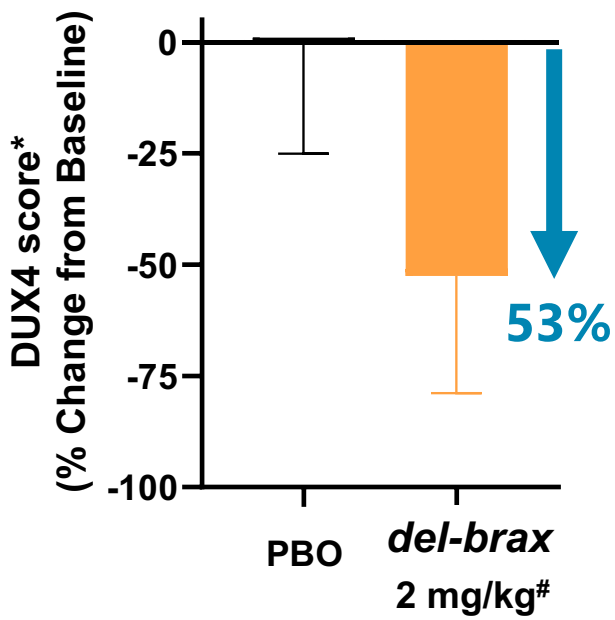
FORTITUDE™

Del-brax Showed Consistent >50% Reductions in DUX4-regulated Genes as Measured by Multiple Gene Panels

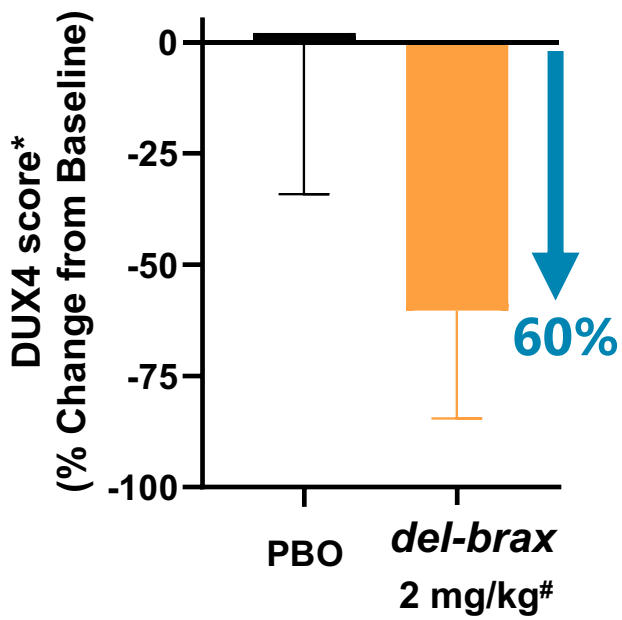
Avidity Panel[1]



ReDux4 Panel[2]



41-Gene Panel[3]



[1] Avidity 4-Gene panel (LEUTX, TRIM43, MBD3L2, KHDC1L; Reference genes: TBP, STATA5)
[2] ReDux4 6-Gene panel (CCNA1, ZSCAN4, MBD3L2, KHDC1L, SLC34A2, PRAMEF6); Tawil, R. et al., *Lancet Neurol* **23**:477 (2024)
[3] Van den Heuvel, A. et al., *Scientific Reports* **12**:1426 (2022)
* DUX4 score in MRI informed muscle biopsy were determined utilizing qPCR (Avidity panel) or RNASeq (ReDux and 41-Gene). DUX4 score calculated as cumulative expression of each gene and data presented as change at 4M treatment relative to cohort normalized baseline. Mean +/- SEM, N=7 *del-brax*, N=4 PBO. One participant in treated group did not receive post-treatment biopsy.
#Doses were 1 mg/kg (D1), 2 mg/kg (D43 and D92) with biopsy 1 month after 3rd dose.

AVIDITY® BIOSCIENCES

FORTITUDE™

Circulating Biomarkers Provide Early Detection of Whole-Body Response to *del-brax* Treatment

Muscle Biopsy

- Sampling of single muscle
- Limited timepoints
- Invasive

Circulating Biomarker

- Comprehensive assessment throughout body
- Continuous monitoring
- Non-invasive

Novel DUX4-Regulated Circulating Biomarker

Potential accelerated approval endpoint

Multi-year Discovery Process

FSHD & Healthy Biopsies

Plasma from FSHD & Healthy Volunteers

Advisors & Disease Expertise

Novel DUX4-Regulated Circulating Biomarker

Potential Accelerated Approval Endpoint

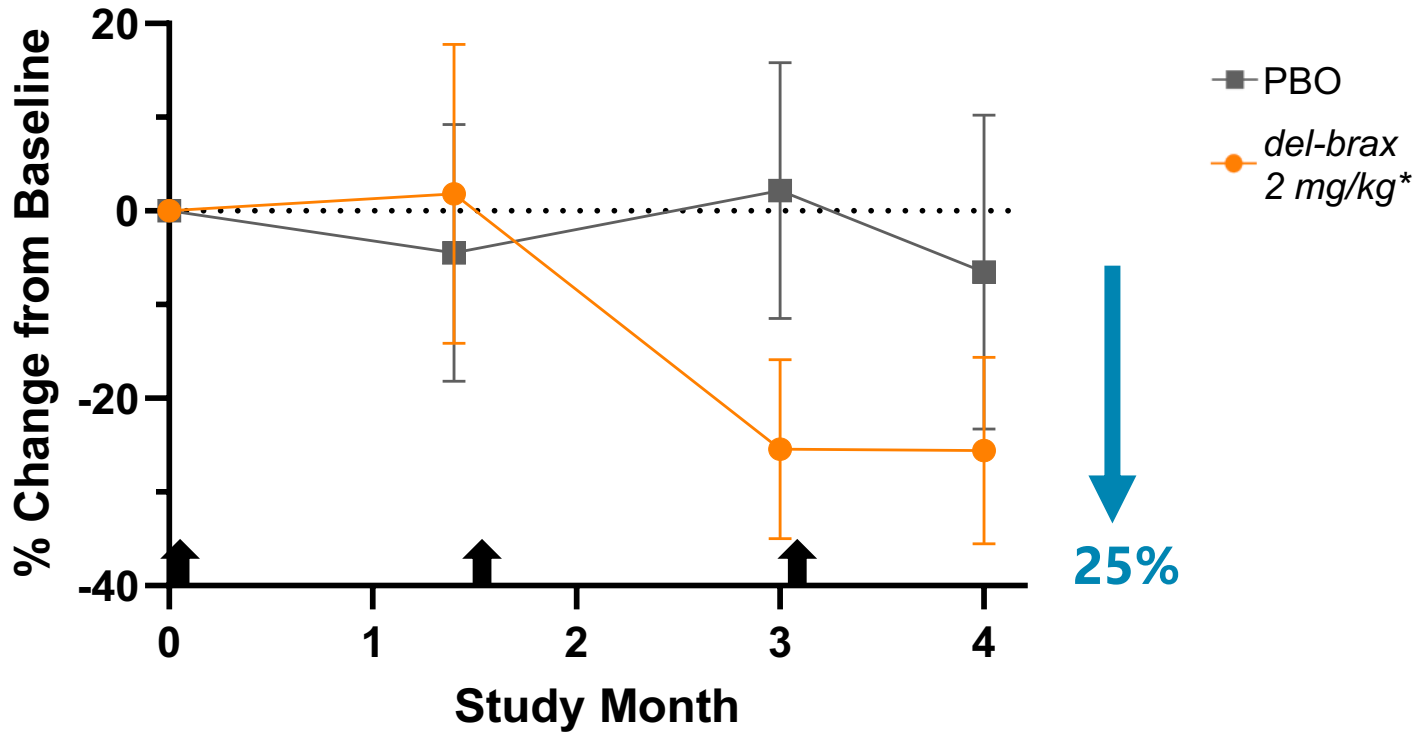
- Significantly elevated in patients with FSHD as compared to healthy individuals
- Allows rapid and continuous monitoring of how participants are responding to *del-brax*
- Non-invasive, patient-friendly
- Guides selection of dose regimen

AVIDITY® BIOSCIENCES

FORTITUDE™

Del-brax Showed Early and Sustained Reduction of a Novel DUX4-Regulated Circulating Biomarker

Del-brax treatment shows 25% reduction in circulating biomarker in participants with FSHD versus placebo

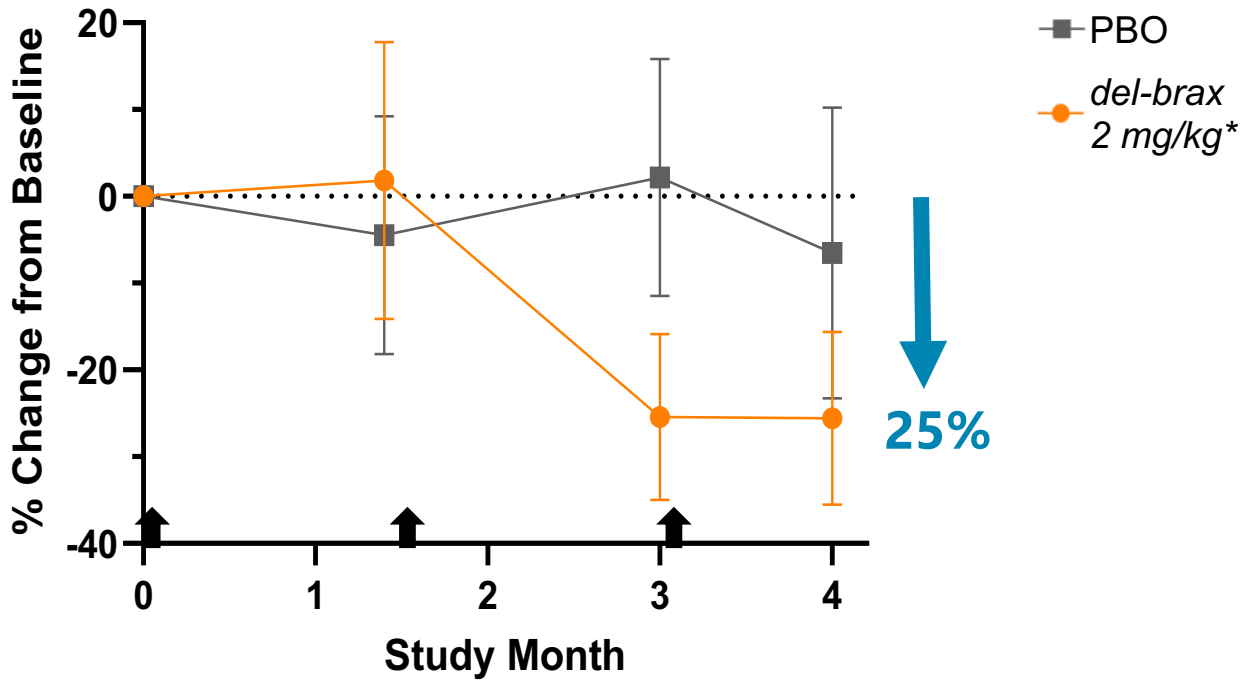


Timecourse of circulating biomarker at baseline and several timepoints post dose
*del-brax dose shown by black arrows 1mg/kg D1, 2 mg/kg D43 and D92. Placebo n=4 and del-brax treated n=8; Mean +/- SEM.

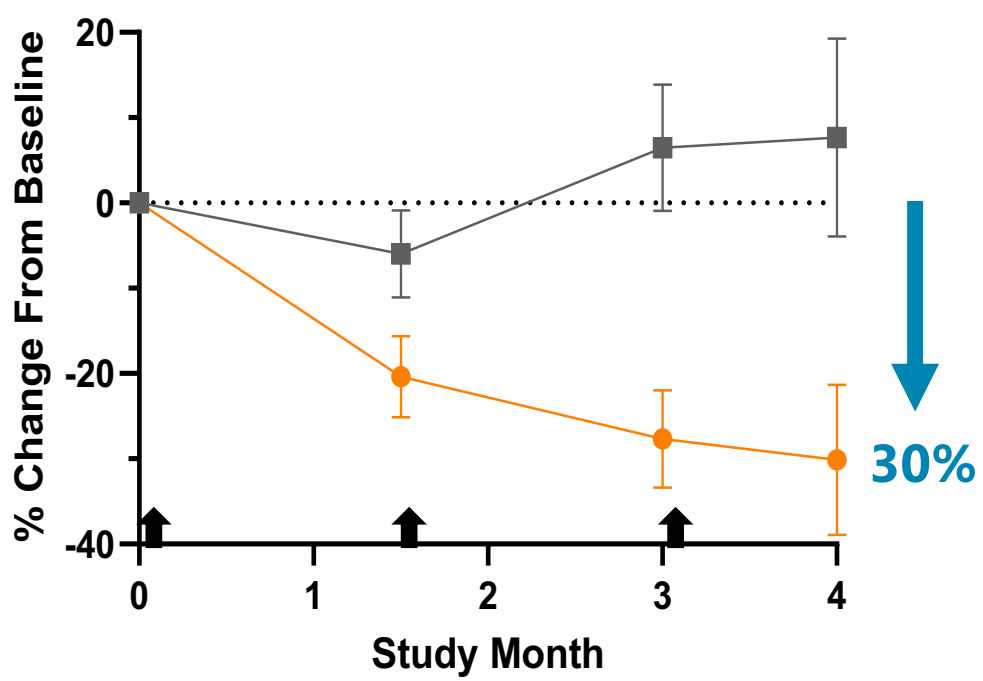
Consistent and Confirmatory Decrease in Both Novel and Creatine Kinase Circulating Biomarkers

Decreases in creatine kinase, an indicator of muscle damage

Novel DUX4-regulated biomarker

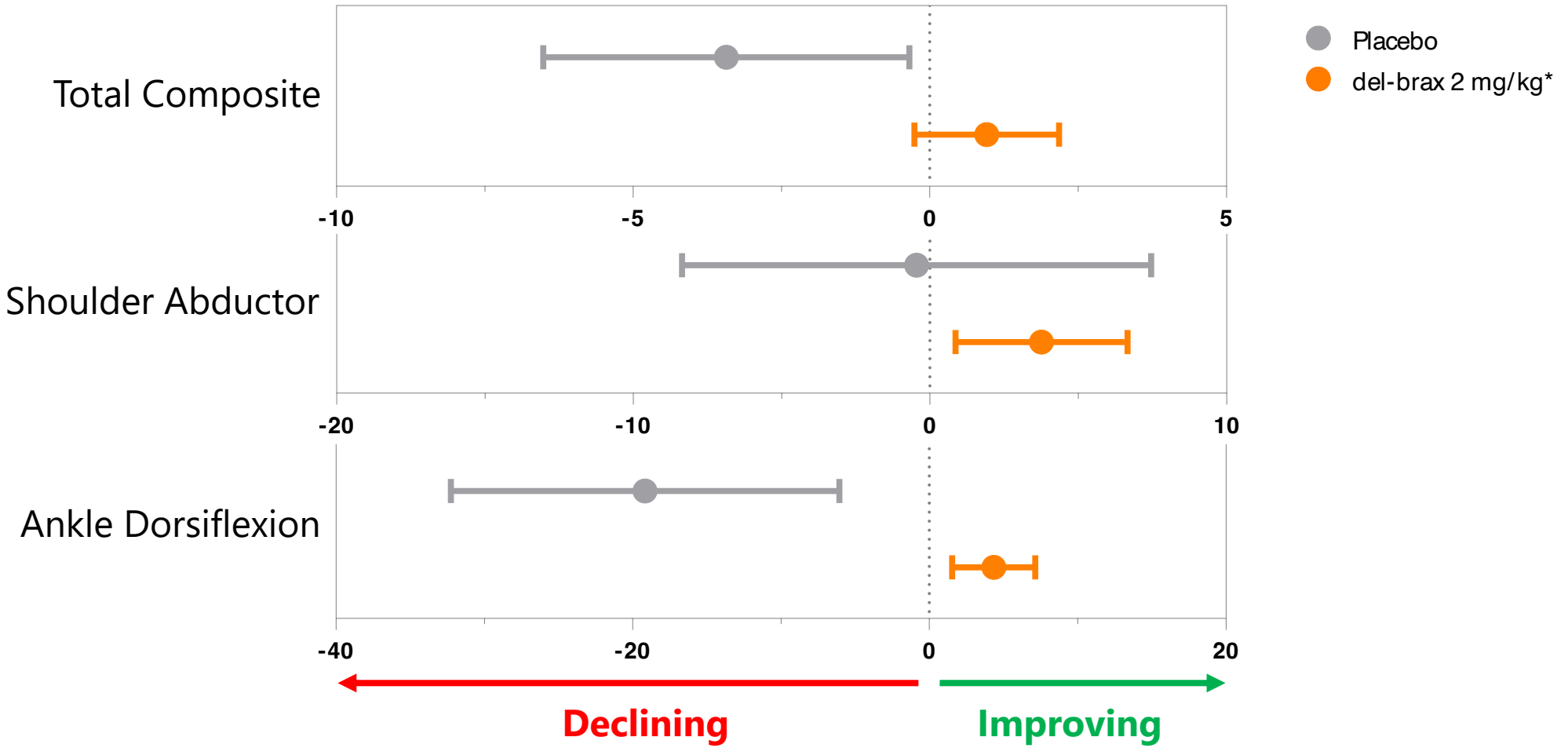


Creatine kinase biomarker



Timecourse of circulating biomarker at baseline and several timepoints post dose
*del-brax dose shown by black arrows 1mg/kg D1, 2 mg/kg D43 and D92. Placebo n=4 and del-brax treated n=8; Mean +/- SEM.

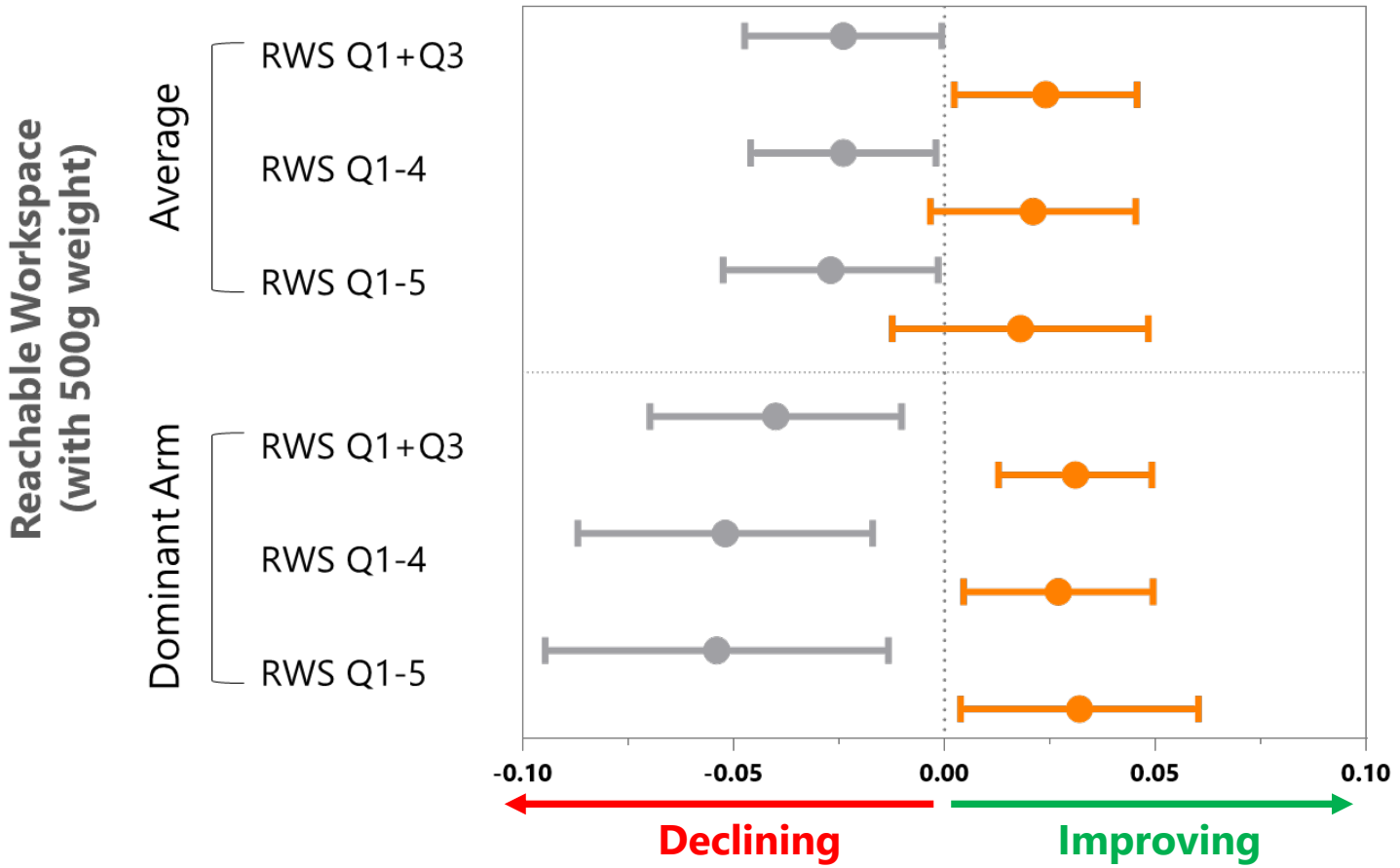
Del-brax Improved Muscle Strength in Both Upper and Lower Limb

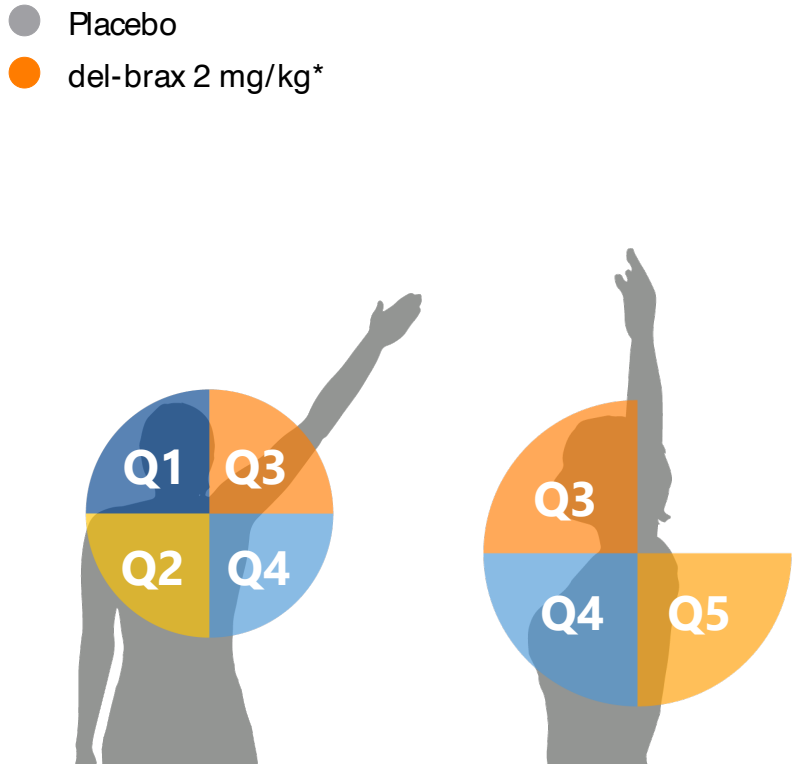


Change from Baseline to Month 4 (Mean ± SEM) Percent Predicted Normal
QMT by hand-held device
Total composite score: shoulder abductors, shoulder external rotators, elbow flexors, elbow extensors, knee flexor, knee extensor and ankle dorsiflexion
* Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study

Del-brax Improved Reachable Workspace Compared to Placebo

Improved range of motion and function; similar trends observed without weight



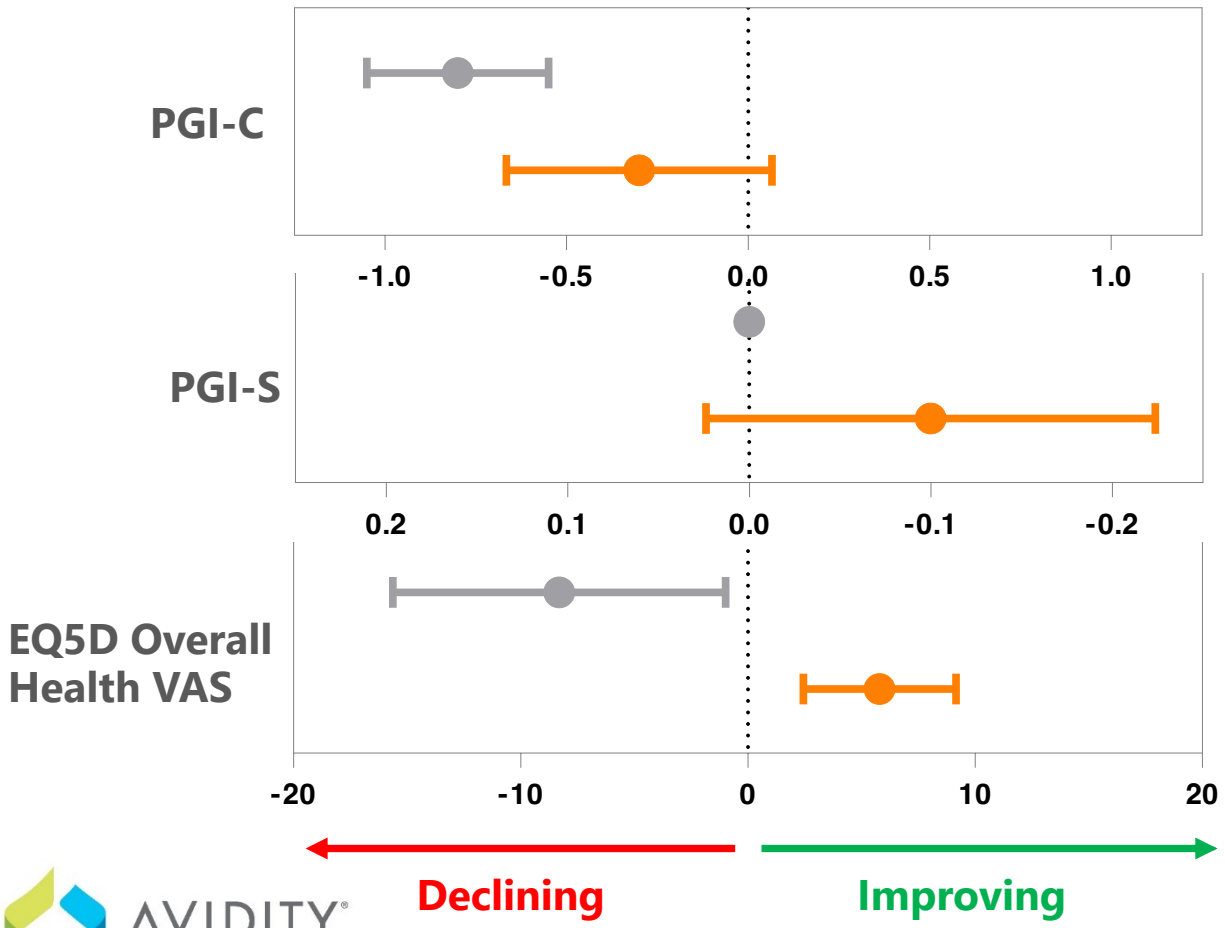


Change from Baseline to Month 4 (Mean ±SEM) Relative Surface Area
Average n=8 & Dominant n=7 in the AOC group
* Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study

Del-brax: Positive Trends Toward Improvement in Both Patient and Clinician Reported Outcome Measures

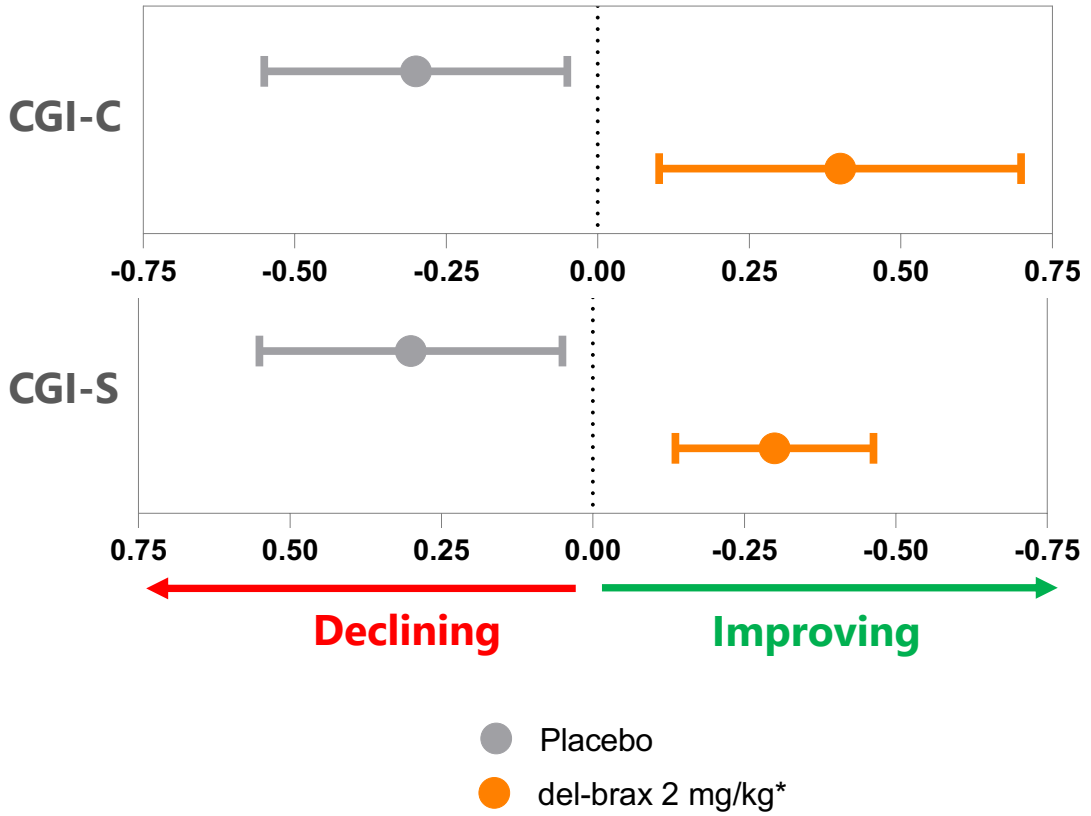
Patient Reported Outcome Measures

Change from Baseline at Month 4 (SEM)



Clinician Reported Outcome Measures

Change from Baseline at Month 4 (SEM)



CGI-C; CGI-S (Clinician Global Impression of Change; Severity)
PGI-C; PGI-S (Patient Global Impression of Change; Severity)
*first dose 1 mg/kg

AVIDITY BIOSCIENCES

FORTITUDE™ 22

Del-brax: Transforming the Treatment of FSHD

Unprecedented & Consistent Reduction in DUX4 Regulated Genes	Signs of Functional Improvement and Reported Outcomes	Favorable Safety and Tolerability
• Greater than 50% reduction across multiple DUX4 gene panels • All treated participants showed reductions greater than 20% • Reduction of a newly-identified DUX4 circulating biomarker & creatine kinase	• Improved muscle strength • Increased reachable workspace compared to placebo and natural history study • Positive patient and clinician reported outcomes	• All adverse events (AEs) were mild or moderate • No serious AE, No severe AE • No discontinuations

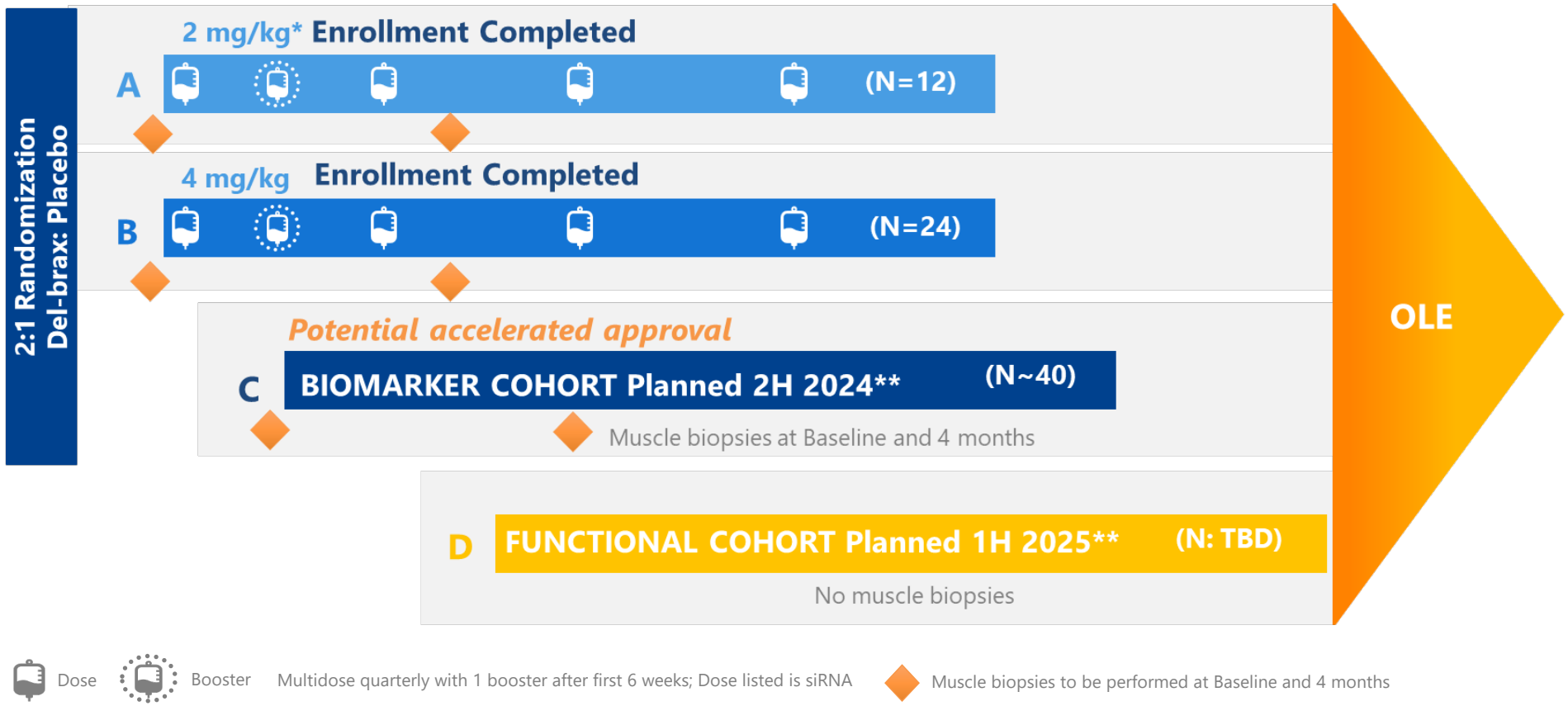
Accelerating *Del-brax* Toward Approval

AVIDITY BIOSCIENCES

FORTITUDE™

Accelerating *Del-brax* Registrational Plan

Partnering with FSHD Society to share more information on FORTITUDE as it becomes available



* Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study
**Dose and schedule to be determined in Q3 2024

Avidity is Committed to Improving the Lives of People Living with FSHD

Connect with us Patients@aviditybio.com

AVIDITY BIOSCIENCES